



Myasthenia Gravis Associated with Nivolumab Therapy in a Patient with Melanoma

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Abstract

Introduction: Immune checkpoint inhibitors exhibit robust antitumor activity in melanoma treatment but can induce highly toxic immunogenic effects. This case details an uncommonly severe adverse reaction to immune therapy and demonstrates the importance of identifying toxicities early to avoid adverse treatment outcomes.

Presentation of Case: We present a patient who received anti-PD1 immunotherapy, nivolumab, as a second-line treatment for stage IV resected melanoma. The patient experienced several immune-related adverse effects and was diagnosed with myasthenia gravis. Despite receiving steroid, immunoglobulin, and plasmapheresis treatment, the patient passed away.

Conclusion: This case highlights the importance of closely monitoring and quickly addressing symptoms of nivolumab toxicity. Rapid institution of immunosuppressive therapy is not always successful.

Keywords: Melanoma; immunotherapy toxicity; adverse effects of immunotherapy

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Consent: Consent was taken from the patient's next of kin for publication of this case report.

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Introduction

While immune check-point inhibitors are highly efficacious in melanoma treatment, they may induce toxic and life-threatening effects[1]. Among immunotherapy treatments indicated for melanoma, the anti-programmed cell death 1 (PD-1) antibody nivolumab has one of the lowest rates of severe adverse events[2,3]. Additionally, nivolumab has shown similar efficacy and toxicity in both young and older, higher-risk patient populations[4]. Despite this efficacy and relative safety, rare and life-threatening adverse events have been reported[3,5–9].

Here we discuss the case of a 75-year-old male experiencing severe immune-related adverse effects including myasthenia gravis (MG) following just two doses of nivolumab treatment. Despite subsequent steroid, immunoglobulin, and plasmapheresis treatments, the patient passed away within months of first experiencing adverse effects. This case adds to the growing number of reports of MG associated with nivolumab treatment and underscores the need for careful observation and aggressive treatment of side effects.

Case Presentation

A 75-year-old male presented with stage IB melanoma (T2aN0M0) localized to the left ear in 2014. The patient underwent a negative margin excision of the tumor with no evidence of disease (NED) remaining. Two years later, the patient received a computed tomography (CT) scan revealing a 3mm nodule in the lung. A CT plus positron emission tomography (PET) scan was performed five months later at which time the tumor had grown to 8mm and exhibited a standardized uptake value (SUV) of 2.7. Due to suspected malignancy, the nodule was resected, and a pathology report revealed malignant melanoma felt to be stage IV with NED. The patient was started on an immune check-point inhibition treatment trial pairing nivolumab together with randomized vaccine or no vaccine. The patient was randomized to the no vaccine group and received a 240mg IV dose of nivolumab every two weeks.

Upon presenting for a third dose of nivolumab, the patient endorsed diplopia, diffuse muscle aching and pain, and shortness of breath. Testing was ordered and the third dose of nivolumab was withheld due to suspected toxicity. The patient was later called into the ER when lab results revealed severely elevated enzyme levels.

Elevated CPK (6674 U/L), LDH (1535 U/L), and Aldolase (123.5 U/L) indicated myositis. Hepatitis and myocarditis were also suspected due to elevated AST/ALT (744/475 U/L) and troponin (2.69) respectively. Steroid treatment with prednisone was initiated. Following hypoxemic respiratory failure days later, the patient was transferred to the critical care unit. Further lab testing revealed normal GGT (20) levels ruling out hepatitis. An MRI of the brain revealed no metastasis and a nerve conduction velocity test indicated no motor neuropathy. These test results eliminated brain metastases and neuritis as potential diagnoses.

Further lab work showed positive acetylcholine receptor antibody (38%), acetylcholine receptor blocking antibody (3.15 nmol/L), and mestinon tests. Based on these results and the clinical picture of diplopia, respiratory weakness, and bulbar weakness, MG was suspected. The patient subsequently received additional steroid and mestinon treatment. Lab results showing normal CPK, AST/ALT, and LDH levels indicated myositis and myocarditis had resolved, however MG symptoms remained. The patient began daily plasmapheresis(x5) and later immunoglobulin(x2) treatment and showed improvement over the following two weeks. The patient was discharged into the care of a nursing home about a month after being admitted into the hospital and passed away shortly thereafter.

Discussion

A literature review revealed six cases previously reported of MG associated with nivolumab treatment for various cancer types. Each of these cases showed a similar clinical picture of fatigue, muscle weakness, and diplopia among other symptoms. In three of the reported cases, the patients recovered following MG treatment. Two of these cases required only mestinon or only prednisone treatment for symptoms to resolve[8,10]. The third case required prednisone, mestinon, immunoglobulin and plasmapheresis to resolve MG-related symptoms. This case was particularly like the one presented here as the patient was also diagnosed with myositis related to nivolumab treatment. However, unlike the case presented, the patient's symptoms arose following just one round of nivolumab treatment. Additionally, these symptoms were resolved following a similar treatment protocol that proved unsuccessful for the patient discussed in this case[11].

Two additional cases of nivolumab-induced MG resulted in patient death following similar treatment protocol used in this case[5,9]. The sixth and final case reported was of a patient who developed MG under a dual nivolumab and ipilimumab treatment protocol[7]. Ipilimumab has previously been associated with MG, but the growing number of nivolumab-related cases reveal the high importance of closely monitoring patient reactions to the drug. Additionally, while previous research has shown no significant difference in immune checkpoint inhibitor toxicity between young and older patients, in all cases discussed here, the patients were over the age of 65[4]. This indicates more research is necessary to determine markers for at risk patients. Lastly, immunosuppressant therapy in combination with nivolumab treatment has been suggested to mitigate potential toxic side-effects. Given the severity of symptoms in this case, immunosuppressant therapy may have been beneficial. Identifying markers for at risk patients would help determine who could benefit from immunosuppressant therapy when receiving nivolumab treatment.

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